

Modern concepts of cholinergic neurotransmission at motor synapses

Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

© 2018 Ruslania. All Rights Reserved. Cholinergic synaptic contact between motor neuron and skeletal muscle fiber is perhaps one of the core objects for investigations of molecular mechanisms underlying the communication between neurons and innervated cells. In the studies conducted on this object in the past few decades, a large amount of experimental data was obtained that substantially complemented a traditional view on synaptic transmission. In particular, it was established that (i) acetylcholine is released from the nerve ending in both quantal and non-quantal ways; (ii) molecular mechanisms of the processes of the quantal acetylcholine release - spontaneous and evoked by electrical stimuli - have unique features and can be regulated independently; (iii) acetylcholine release from the nerve ending is accompanied by a release of a number of synaptically active molecules modulating the processes of secretion or reception of the main mediator; (iv) signal molecules affecting the process of cholinergic neurosecretion can be released not only from the nerve ending but also from glial cells and muscle fiber; (v) molecular mechanisms of the regulation of synaptic transmission are highly diverse and go beyond the alteration of the number of the released acetylcholine quanta. Thus, the neuromuscular junction shall be deemed currently as complicated and adaptive synapse characterized by a wide range of multi-loop intercellular signaling pathways between presynaptic motor neuron ending, muscle fiber, and glial cells ensuring a high safety factor of synaptic transmission and the possibility of its fine tuning.

Keywords

Cholinergic synapse, Cotransmission, Neuromodulators, Quantal and non-quantal release of mediator, Synaptic plasticity

References

- [1] Sarter M., Hasselmo M.E., Bruno J.P., Givens B. 2005. Unraveling the attentional functions of cortical cholinergic inputs: interactions between signal-driven and cognitive modulation of signal detection. *Brain Res. Brain Res. Rev.* 48 (1), 98-111.
- [2] Hasselmo M.E. 2006. The role of acetylcholine in learning and memory. *Curr. Opin. Neurobiol.* 16 (6), 710-715.
- [3] Salpeter M.M. 1987. *The vertebrate neuromuscular junction*. New York: Alan R. Liss Inc., 440 p.
- [4] Hall Z.W., Sanes J.R. 1993. Synaptic structure and development: The neuromuscular junction. *Cell*. 72, Suppl. P. 99-121.
- [5] Hughes B.W., Kusner L.L., Kaminski H.J. 2006. Molecular architecture of the neuromuscular junction. *Muscle Nerve*. 33 (4), 445-461.
- [6] Delbono O. 2003. Neural control of aging skeletal muscle. *Aging Cell*. 2 (1), 21-29.

- [7] Lu B., Je H.S. 2003. Neurotrophic regulation of the development and function of the neuromuscular synapses. *J. Neurocytol.* 32, 931-941.
- [8] Wu H., Xiong W.C., Mei L. 2010. To build a synapse: signaling pathways in neuromuscular junction assembly. *Development.* 137 (7), 1017-1033.
- [9] Fatt P., Katz B. 1952. Spontaneous subthreshold activity at motor nerve endings. *J. Physiol.* 117(1), 109-128.
- [10] Del Castillo J., Katz B. 1954. Quantal components of the end-plate potential. *J. Physiol.* 124 (3), 560-573.
- [11] Malomouzh A.I., Mukhtarov M.R., Nikolsky E.E., Vyskocil F. 2007. Muscarinic M1 acetylcholine receptors regulate the non-quantal release of acetylcholine in the rat neuromuscular junction via NO-dependent mechanism. *J. Neurochem.* 102 (6), 2110-2117.
- [12] Malomouzh A.I., Petrov K.A., Nurullin L.F., Nikolsky E.E. 2015. Metabotropic GABAB receptors mediate GABA inhibition of acetylcholine release in the rat neuromuscular junction. *J. Neurochem.* 135 (6), 1149-1160.
- [13] VanderKloot W. 2003. Loading and recycling of synaptic vesicles in the Torpedo electric organ and the vertebrate neuromuscular junction. *Prog. Neurobiol.* 71 (4), 269-303.
- [14] Sudhof T.C. 2004. The synaptic vesicle cycle. *Annu. Rev. Neurosci.* 27, 509-547.
- [15] Tremblay J.P., Laurie R.E., Colonnier M. 1983. Is the M EPP due to the release of one vesicle or to the simultaneous release of several vesicles at one active zone? *Brain Res.* 287 (3), 299-314.
- [16] He L., Wu L.G. 2007. The debate on the kiss-and-run fusion at synapses. *Trends Neurosci.* 30 (9), 447-55.
- [17] Bertone N.I., Groisman A.I., Mazzone G.L., Cano R., Tabares L., Uchitel O.D. 2017. Carbonic anhydrase inhibitor acetazolamide shifts synaptic vesicle recycling to a fast mode at the mouse neuromuscular junction. *Synapse.* 71 (12), doi: 10.1002/syn.22009.
- [18] Alabi A.A., Tsien R.W. 2013. Perspectives on kiss- and-run: role in exocytosis, endocytosis, and neurotransmission. *Annu. Rev. Physiol.* 75, 393-422.
- [19] Thesleff S. 1986. Different kinds of acetylcholine release from the motor nerve. *Int. Rev. Neurobiol.* 28, 59-88.
- [20] Thesleff S. 1990. Functional aspects of quantal and non-quantal release of acetylcholine at the neuromuscular junction. *Prog. Brain Res.* 84, 93-99.
- [21] Clayton E.L., Cousin M.A. 2009. The molecular physiology of activity-dependent bulk endocytosis of synaptic vesicles. *J. Neurochem.* 111 (4), 901-914.
- [22] Gaydukov A.E., Bogacheva P.O., Tarasova E.O., Balezina O.P. 2014. The mechanism of choline-mediated inhibition of acetylcholine release in mouse motor synapses. *Acta Naturae.* 6 (4), 110-115.
- [23] Thyagarajan B., Potian J.G., Baskaran P., McArdle J.J. 2014. Capsaicin modulates acetylcholine release at the myoneural junction. *Eur. J. Pharmacol.* 744, 211-219.
- [24] Glitsch M. 2006. Selective inhibition of spontaneous but not Ca²⁺-dependent release machinery by presynaptic group 11 mGluRs in rat cerebellar slices. *J. Neurophysiol.* 96 (1), 86-96.
- [25] Pratt K.G., Zhu P., Watari H., Cook D.G., Sullivan J.M. 2011. A novel role for γ -secretase: selective regulation of spontaneous neurotransmitter release from hippocampal neurons. *J. Neurosci.* 31 (3), 899-906.
- [26] Pan Z.H., Segal M.M., Lipton S.A. 1996. Nitric oxide-related species inhibit evoked neurotransmission but enhance spontaneous miniature synaptic currents in central neuronal cultures. *Proc. Natl. Acad. Sci. USA.* 93 (26), 15423-15428.
- [27] Wasser C.R., Ertunc M., Liu X., Kavalali E.T. 2007. Cholesterol-dependent balance between evoked and spontaneous synaptic vesicle recycling. *J. Physiol.*, 579, 413-429.
- [28] Ramirez D.M., Kavalali E.T. 2011. Differential regulation of spontaneous and evoked neurotransmitter release at central synapses. *Curr. Opin. Neurobiol.* 21 (2), 275-282.
- [29] Walter A.M., Haucke V., Sigrist S.J. 2014. Neurotransmission: spontaneous and evoked release filing for divorce. *Curr. Biol.* 24, R192-194.
- [30] Mitchell J.F., Silver A. 1963. The spontaneous release of acetylcholine from the denervated hemidiaphragm of the rat. *J. Physiol.* 165 (1), 117-129.
- [31] Fletcher P., Forrester T. 1975. The effect of curare on the release of acetylcholine from mammalian motor nerve terminals and an estimate of quantum content. *J. Physiol.* 251 (1), 131-144.
- [32] Vizi E.S., Vyskocil F. 1979. Changes in total and quantal release of acetylcholine in the mouse diaphragm during the inhibition of membrane ATPase. *J. Physiol.* 286, 1-14.
- [33] Fu W.-M., Liou H.-C., Chen Yu-H., Wang S.-M. 1998. Release of acetylcholine from embryonic myocytes in *Xenopus* cell cultures. *J. Physiol.* 509 (2), 497-506.
- [34] Katz B., Miledi R. 1977. Transmitter leakage from motor nerve endings. *Proc. R. Soc. London Ser. B.* 196, 59-72.
- [35] Vyskocil F., Illes P. 1977. Non-quantal release of transmitter at mouse neuromuscular junction and its dependence on the activity of Na⁺-K⁺ ATP-ase. *Pflugers Arch.* 370 (3), 295-297.
- [36] Nikolsky E.E., Oranska T.I., Vyskocil F. 1996. Non-quantal acetylcholine release in the mouse diaphragm after phrenic nerve crush and during recovery. *Exp. Physiol.* 81 (3), 341-348.

- [37] Vyskocil F., Nikolsky E., Edwards C. 1983. An analysis of the mechanisms underlying the non-quantal release of acetylcholine at the mouse neuromuscular junction. *Neuroscience*. 9 (2), 429-435.
- [38] Nikolsky E.E., Voronin V.A., Oranska T.I., Vyskocil F. 1991. The dependence of non-quantal acetylcholine release on the choline-uptake system in the mouse diaphragm. *Pflügers Arch.* 418 (1-2), 74-78.
- [39] Linden D.C., Newton M.W., Grinnell A.D., Jenden D.J. 1983. Rapid decline in acetylcholine release and content of rat extensor digitorum longus muscle after denervation. *Exp. Neurol.* 81 (3), 613-626.
- [40] Sun Y.-A., Poo M.-M. 1985. Non-quantal release of acetylcholine at a developing neuromuscular synapse in culture. *J. Neurosci.* 5 (3), 634-642.
- [41] Vyskocil F., Vrbova G. 1993. Non-quantal release of acetylcholine affects polyneuronal innervation on developing rat muscle fibres. *Eur. J. Neurosci.* 5 (12), 1677-1683.
- [42] Minic J., Molgo J., Karlsson E., Krejci E. 2002. Regulation of acetylcholine release by muscarinic receptors at the mouse neuromuscular junction depends on the activity of acetylcholinesterase. *Eur. J. Neurosci.* 15 (3), 439-448.
- [43] Edwards R.H. 2007. The neurotransmitter cycle and quantal size. *Neuron*. 55 (6), 835-858.
- [44] Edwards C., Dolezal V., Tucek S., Zemkova H., Vyskocil F. 1985. Is an acetylcholine transport system responsible for nonquantal release of acetylcholine at the rodent myoneural junction? *Proc. Natl. Acad. Sci. USA*. 82(10), 3514-3518.
- [45] Vyskocil F., Malomouzh A., Nikolsky E. 2009. Non-quantal acetylcholine release at the neuromuscular junction. *Physiol. Res.* 58 (6), 763-784.
- [46] Attwell D., Barbour B., Szatkowski M. 1993. Nonvesicular release of neurotransmitter. *Neuron*. 11 (3), 401-407.
- [47] Bray J. J., Forrest J.W., Hubbard J.I. 1982. Evidence for the role of non-quantal acetylcholine in the maintenance of the membrane potential of rat skeletal muscle. *J. Physiol.* 326, 285-296.
- [48] Urazaev A., Naumenko N., Malomouzh A., Nikolsky E., Vyskocil F. 2000. Carbachol and acetylcholine delay the early postdenervation depolarization of muscle fibres through M 1-cholinergic receptors. *Neurosci. Res.* 37 (4), 255-263.
- [49] Vyskocil F. 2003. Early postdenervation depolarization is controlled by acetylcholine and glutamate via nitric oxide regulation of the chloride transporter. *Neurochem. Res.* 28 (3-4), 575-585.
- [50] Nikolsky E.E., Zemkova H., Voronin V.A., Vyskocil F. 1994. Role of non-quantal acetylcholine release in surplus polarization of mouse diaphragm fibres at the end-plate zone. *J. Physiol.* 477, 497-502.
- [51] Chdvez J., Vargas M.H., Cruz-Valderrama J.E., Montafio L.M. 2011. Non-quantal release of acetylcholine in guinea-pig airways: role of choline transporter. *Exp. Physiol.* 96 (4), 460-467.
- [52] Abramochkin D.V., Nurullin L.F., Borodinova A.A., Tarasova N.V., Sukhova G.S., Nikolsky E.E., Rosenshtaukh L.V. 2010. Non-quantal release of acetylcholine from parasympathetic nerve terminals in the right atrium of rats. *Exp. Physiol.* 95 (2), 265-273.
- [53] Abramochkin D.V., Borodinova A.A., Rosenshtaukh L.V. 2012. Effects of acetylcholinesterase inhibitor paraoxon denote the possibility of non-quantal acetylcholine release in myocardium of different vertebrates. *J. Comp. Physiol. B.* 182 (1), 101-108.
- [54] Burnstock G. 2004. Cotransmission. *Curr. Opin. Pharmacol.* 4 (1), 47-52.
- [55] Burnstock G. 2009. Autonomic neurotransmission: 60 years since sir Henry Dale. *Annu. Rev. Pharmacol. Toxicol.* 49, 1-30.
- [56] Gutierrez R. 2009. Co-Existence and Co-Release of Classical Neurotransmitters. New York: Springer, 275 p.
- [57] Silinsky E.M. 1975. On the association between transmitter secretion and the release of adenine nucleotides from mammalian motor nerve terminals. *J. Physiol.* 247 (1), 145-162.
- [58] Burnstock G. 2007. Physiology and pathophysiology of purinergic neurotransmission. *Physiol. Rev.* 87 (2), 659-797.
- [59] Santos D.A., Salgado A.I., Cunha R.A. 2003. ATP is released from nerve terminals and from activated muscle fibres on stimulation of the rat phrenic nerve. *Neurosci. Lett.* 338 (3), 225-228.
- [60] Todd K.J., Darabid H., Robitaille R. 2010. Perisynaptic glia discriminate patterns of motor nerve activity and influence plasticity at the neuromuscular junction. *J. Neurosci.* 30 (35), 11870-11882.
- [61] Bao L., Locovei S., Dahl G. 2004. Pannexin membrane channels are mechanosensitive conduits for ATP. *FEBS Lett.* 572 (1-3), 65-68.
- [62] Dahl G. 2015. ATP release through pannexon channels. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 370 (1672), pii: 20140191.
- [63] Tung E.K., Choi R.C., Siow N.L., Jiang J.X., Ling K.K., Simon J., Barnard E.A., Tsim K.W. 2004. P2Y2 receptor activation regulates the expression of acetylcholinesterase and acetylcholine receptor genes at vertebrate neuromuscular junctions. *Mol. Pharmacol.* 66 (4), 794-806.

- [64] Ling K.K., Siow N.L., Choi R.C., Ting A.K., Kong L.W., Tsim K.W. 2004. ATP potentiates agrin- induced AChR aggregation in cultured myotubes: Activation of RhoA in P2Y1 nucleotide receptor signaling at vertebrate neuromuscular junctions. *J. Biol. Chem.* 279 (30), 31081-31088.
- [65] Ryten M., Koshi R., Knight G.E., Turmaine M., Dunn P., Cockayne D.A., Ford A.P., Burnstock G. 2007. Abnormalities in neuromuscular junction structure and skeletal muscle function in mice lacking the P2X2 nucleotide receptor. *Neuroscience*. 148 (3), 700-711.
- [66] Malomouzh A.I., Nikolsky E.E., Vyskocil F. 2011. Purine P2Y receptors in ATP-mediated regulation of non-quantal acetylcholine release from motor nerve endings of rat diaphragm. *Neurosci. Res.* 71 (3), 219-225.
- [67] Danbolt N.C. 2001. Glutamate uptake. *Prog. Neurobiol.* 65 (1), 1-105.
- [68] Waerhaug O., Ottersen O.P. 1993. Demonstration of glutamate-like immunoreactivity at rat neuromuscular junctions by quantitative electron microscopic immunocytochemistry. *Anat. Embryol. (Berl.)* 188 (5), 501-513.
- [69] Kerkut G.A., Shapira A., Walker R.J. 1967. The transport of ¹⁴C-labelled material from CNS to and from muscle along a nerve trunk. *Comp. Biochem. Physiol.* 23 (3), 729-748.
- [70] Fu W.M., Liou J.C., Lee Y.H., Liou H.C. 1995. Potentiation of neurotransmitter release by activation of presynaptic glutamate receptors at developing neuromuscular synapses of *Xenopus*. *J. Physiol.* 489., 813-823.
- [71] Pinard A., Robitaille R. 2008. Nitric oxide dependence of glutamate-mediated modulation at a vertebrate neuromuscular junction. *Eur. J. Neurosci.* 28 (3), 577-587.
- [72] Mays T.A., Sanford J.L., Hanada T., Chishti A.H., Rafael-Fortney J.A. 2009. Glutamate receptors localize postsynaptically at neuromuscular junctions in mice. *Muscle Nerve*. 39 (3), 343-349.
- [73] Malomouzh A.I., Nurullin L.F., Arkhipova S.S., Nikolsky E.E. 2011. NMDA receptors at the endplate of rat skeletal muscles: precise postsynaptic localization. *Muscle Nerve*. 44 (6), 987-989.
- [74] Malomouzh A.I., Mukhtarov M.R., Nikolsky E.E., Vyskocil F., Lieberman E.M., Urazaev A.K. 2003. Glutamate regulation of non-quantal release of acetylcholine in the rat neuromuscular junction. *J. Neurochem.* 85(1), 206-213.
- [75] Stamler J.S., Meissner G. 2001. Physiology of nitric oxide in skeletal muscle. *Physiol. Rev.* 81 (1), 209-237.
- [76] Neale J.H., Bzdega T., Wroblewska B. 2000. N-Acetylglutamate: The most abundant peptide neurotransmitter in the mammalian central nervous system. *J. Neurochem.* 75 (2), 443-452.
- [77] Berger U.V., Carter R.E., Coyle J.T. 1995. The immunocytochemical localization of N-acetylglutamate, its hydrolysing enzyme NAALADase, and the NMDAR-1 receptor at a vertebrate neuromuscular junction. *Neuroscience*. 64 (4), 847-850.
- [78] Malomouzh A.I., Nikolsky E.E., Lieberman E.M., Sherman J.A., Lubischer J.L., Grossfeld R.M., Urazaev A. Kh. 2005. Effect of N-acetylglutamate (NAAG) on non-quantal and spontaneous quantal release of acetylcholine at the neuromuscular synapse of rat. *J. Neurochem.* 94 (1), 257-267.
- [79] Walder K.K., Ryan S.B., Bzdega T., Olszewski R.T., Neale J.H., Lindgren C.A. 2013. Immunohistological and electrophysiological evidence that N-acetylglutamate is a co-transmitter at the vertebrate neuromuscular junction. *Eur. J. Neurosci.* 237 (1), 118-129.
- [80] Datar P., Srivastava S., Coutinho E., Govil G. 2004. Substance P: structure, function, and therapeutics. *Curr. Top. Med. Chem.* 4 (1), 75-103.
- [81] Matteoli M., Haimann C., DeCamilli P. 1990. Substance P-like immunoreactivity at the frog neuromuscular junction. *Neuroscience*. 37(1), 271-275.
- [82] Gundersen K., Oktedalen O., Fonnum F. 1985. Substance P in subdivisions of the sciatic nerve, and in red and white skeletal muscles. *Brain Res.* 329 (1-2), 97-103.
- [83] Akasu T. 1986. The effects of substance P on neuromuscular transmission in the frog. *Neurosci. Res.* 3 (4), 275-284.
- [84] Giniatullin R.A., Zefirov A.L., Magazanik L.G., Oshchepkova S.F. 1991. Postsynaptic effects of substance P in frog neuromuscular junction. *Neurophysiology*. 23, 318-322.
- [85] Bourque M.J., Robitaille R. 1998. Endogenous peptidergic modulation of perisynaptic Schwann cells at the frog neuromuscular junction. *J. Physiol.* 512, 197-209.
- [86] Ganguly D.K., Das M., DasGupta A.K., Chauhan S.P. 1987. Possible functional role of substance P on the mammalian motor nerve terminals. *Life Sci.* 40 (3), 289-292.
- [87] Sala C., Andreose J.S., Fumagalli G., Lomo T. 1995. Calcitonin gene-related peptide: possible role in formation and maintenance of neuromuscular junctions. *Neurosci.* 15, 520-528.
- [88] Laufer R., Changeux J.P. 1989. Calcitonin gene-related peptide and cyclic AMP stimulate phosphoinositide turnover in skeletal muscle cells. Interaction between two second messenger systems. *J. Biol. Chem.* 264 (5), 2683-2689.
- [89] Fontaine B., Klarsfeld A., Changeux J.P. 1987. Calcitonin gene-related peptide and muscle activity regulate acetylcholine receptor alpha-subunit mRNA levels by distinct intracellular pathways. *J. Cell Biol.* 105 (3), 1337-1342.

- [90] Rossi S.G., Dickerson I.M., Rotundo R.L. 2003. Localization of the calcitonin gene-related peptide receptor complex at the vertebrate neuromuscular junction and its role in regulating acetylcholinesterase expression. *J. Biol. Chem.* 278 (27), 2494-5000.
- [91] Takami K., Kawai Y., Uchida S., Tohyama M., Shiotani Y., Yoshida H., Emson P.C., Girgis S., Hillyard C.J., MacIntyre L. 1985. Effect of calcitonin gene-related peptide on contraction of striated muscle in the mouse. *Neurosci. Lett.* 60 (2), 227-230.
- [92] VanderKloot W., Benjamin W.B., Balezina O.P. 1998. Calcitonin gene-related peptide acts presynaptically to increase quantal size and output at frog neuromuscular junctions. *J. Physiol.* 507, 689-695.
- [93] Gaydukov A.E., Bogacheva P.O., Balezina O.P. 2016. Calcitonin gene-related peptide increases acetylcholine quantal size in neuromuscular junctions of mice. *Neurosci. Lett.* 628, 17-23.
- [94] Luck G., Hoch W., Hopf C., Blottner D. 2000. Nitric oxide synthase (NOS-1) coclustered with agrin-induced AChR-specializations on cultured skeletal myotubes. *Mol. Cell. Neurosci.* 16 (3), 269-281.
- [95] Kobzik L., Stringer B., Balligand J.L., Reid M.B., Stamler J.S. 1995. Endothelial type nitric oxide synthase in skeletal muscle fibers: mitochondrial relationships. *Biochem. Biophys. Res. Commun.* 211 (2), 375-381.
- [96] Balon T.W., Nadler J.L. 1997. Evidence that nitric oxide increases glucose transport in skeletal muscle. *J. Appl. Physiol.* 82 (1), 359-363.
- [97] Wolosker H., Panizzutti R., Engelender S. 1996. Inhibition of creatine kinase by S-nitrosoglutathione. *FEBS Lett.* 392 (3), 274-276.
- [98] Kobzik L., Reid M.B., Bredt D.S., Stamler J.S. 1994. Nitric oxide in skeletal muscle. *Nature.* 372 (6506), 546-548.
- [99] Morrison R.J., Miller C.C. III, Reid M.B. 1998. Nitric oxide effects on force-velocity characteristics of the rat diaphragm. *Comp. Biochem. Physiol. A Mol. Integr. Physiol.* 119 (1), 203-209.
- [100] Ambiel C.R., Alves-Do-Prado W. 1997. Neuromuscular facilitation and blockade induced by L-arginine and nitric oxide in the rat isolated diaphragm. *Gen. Pharmacol.* 28 (5), 789-794.
- [101] Thomas S., Robitaille R. 2001. Differential frequency-dependent regulation of transmitter release by endogenous nitric oxide at the amphibian neuromuscular synapse. *J. Neurosci.* 21 (4) 1087-1095.
- [102] Mukhtarov M.R., Urazaev A.K., Nikolsky E.E., Vyskocil F. 2000. Effect of nitric oxide and NO synthase inhibition on nonquantal acetylcholine release in the rat diaphragm. *Eur. J. Neurosci.* 12 (3), 980-986.
- [103] Petrov K.A., Malomouzh A.I., Kovyazina I.V., Krejci E., Nikitashina A.D., Proskurina S.E., Zobov V.V., Nikolsky E.E. 2013. Regulation of acetylcholinesterase activity by nitric oxide in rat neuromuscular junction via N-methyl-D-aspartate receptor activation. *Eur. J. Neurosci.* 37 (2), 181-189.
- [104] Sakuma K., Yamaguchi A. 2011. The recent understanding of the neurotrophin's role in skeletal muscle adaptation. *J. Biomed. Biotechnol.* 2011:201696.
- [105] Pitts E.V., Potluri S., Hess D.M., Balice-Gordon R.J. 2006. Neurotrophin and Trk-mediated signaling in the neuromuscular system. *Int. Anesthesiol. Clin.* 44 (2), 21-76.
- [106] Zhan W.Z., Mantilla C.B., Sieck G.C. 2003. Regulation of neuromuscular transmission by neurotrophins. *Acta Physiologica Sinica.* 55 (6), 617-624.
- [107] Citri A., Malenka R.C. 2008. Synaptic plasticity: multiple forms, functions, and mechanisms. *Neuropsychopharmacology* 33(1), 18-41.
- [108] Wood S.J., Slater C.R. 2001. Safety factor at the neuromuscular junction. *Prog. Neurobiol.* 64 (4), 393-429.
- [109] Pan B., Zucker R.S. 2009. A general model of synaptic transmission and short-term plasticity. *Neuron.* 62 (4), 539-554.
- [110] Lin J.W., Faber D.S. 2002. Modulation of synaptic delay during synaptic plasticity. *Trends Neurosci.* 25 (9), 449-455.
- [111] Lee A.M., Wu D.F., Dadgar J., Wang D., McMahon T., Messing R.O. 2015. PKC ϵ phosphorylates $\alpha 4\beta 2$ nicotinic ACh receptors and promotes recovery from desensitization. *Br. J. Pharmacol.* 172 (17), 4430-4441.